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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/527,919	03/17/2000	Steven Neville Chatfield	KCO1002US	3175

7590 08/13/2003

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EXAMINER
LI, BAO Q

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 08/13/2003

27

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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Paper No. 27

Application Number: 09/527,919

Filing Date: March 17, 2000

Appellant(s): CHATFIELD, STEVEN NEVILLE

Thomas e Popovich & Wiles PA

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on June 10, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims s 35 to 38, 40 to 44 and 46 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

EP-A-A-0 389 983A2	Mimms et al.	March 23, 1990
WO 94/03615A1	Khan et al.	February 1994

Shi et al. "Gene fusion of cholera toxin B subunit and HBV PreS2 epitope and the antigenicity of fusion protein." Vaccine, Vol. 13, no. 10, 1995, pp. 933-937.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 35 to 38, 40 to 44 and 46 are rejected under 35 U.S.C. 103 (a) over Khan et al. (WO 94/03615A), Mimms et al. (EP-A-A-0 389 983A2) and Shi et al. (Vaccine, Vol. 13, no. 10, 1995, pp. 933-937). This rejection is set forth in prior Office Action, Paper Nos 14, 19 and 22.

Khan et al. disclose a fusion protein made by carrier protein Tetanus Toxin C fragment (tetC) or its fragment fused with other antigenic protein or antigenic peptide. They teach that tetC can be fused with HBV for inducing a good immune response against HBV (page 5, line 10 through page 6, line 4). Khan et al. differ from the claimed invention in that they do not precisely teach which HBV surface antigen is fused with TetC.

Initially, Appellant filed a Declaration under 37 CFR 1.132 filed on April 17, 2002 and argue that Dr. Page's Declaration points out that there are a vast number of combinations of carrier and antigenic sequence that could in theory have been dreamt up by a person skilled in the art. Out of all these possible combinations, there was no motivation in the art whatsoever to focus on both fragment C and pre-S1 and put them together. This specific selection was not an obvious selection when viewed in the "real life" context of all the other combinations that a person skilled in the art might in theory have put together.

In response to Applicants' argument, Office indicates that Dr. Page's Declaration is insufficient to overcome the rejection because Khan et al. teach that TetC has been extensively used as an adjuvant for a chemically coupled guest protein or epitope to promoter the immune response of the carried guest protein and epitope (See lines 4-2 on page 3), and they also disclose that a recombinant fusion protein made by fusing TetC with an antigenic protein or peptide produces a good immunogenicity (See lines 25-26 on page 3 and lines 1-8 on page 4).

Appellants further argue that Khan et al. suggests that "fusion two proteins together often leads to an incorrectly fold chimeric protein which no longer retains the properties of the individual components and the efficacy of TetC was not same in all groups.

Appellants' arguments have been fully considered but they are not persuasive because Khan et al. teach that they found a method for overcoming the aforementioned problem. The method is to use an inducible prompter and incorporate a flexible hinge linker between two

antigenic components of the fusion protein. The resulting recombinant antigens have been shown to be efficiently expressed and have a good immunity when the guest gene coding for the protein is linked to TetC at its C terminus (Fig. 2-3). According to the disclosure of the specification (See lies 5-11 on page 15), Appellants also use the same approach as taught by Khan et al. to make the TetC/ HBV pre-S1 fusion protein by using a hinge linker, and operably linked to a promoter, wherein the HBV Pre-S1 antigen epitope is linked to the C-terminus of TetC through the hinge linker. Therefore, the recombinant fusion HBV surface antigen made by the method of Khan et al. gets an enhanced expression and good immunity response results as expected.

Appellants also argue that the mention of hepatitis B in Khan et al.'s reference is just a laundry list and no specific antigenic sequence is mentioned. The skilled person would not be able to derive from Khan et al. teaching to select a suitable hepatitis antigen to include in such a fusion protein.

Appellants' argument has been considered; however, it is not persuasive because the precise structures of HBV surface antigen including pre-S1 or pre-S2 antigenic or epitope are all well documented in the art. Such as Mimms et al. teach several distinct immunogenic epitopes of HBV pre-S1 or Pre-S2. One of the HBV pre-S1 antigen epitope disclosed by Mimms et al. is the pre-S1 located at the amino acid residues from 27-35 (8 contiguous amino acid) or 72 to 102 (30 contiguous amino acids) (See Table 1 on page 4), which is in the range of at least 6 or 20 contiguous amino acids as recited in the rejected claims 35-36, 38, 41-42 and 44. The epitope of amino acids from 27-35 is within the range of amino acid residues of 21 to 47 as recited in claims 37 and 43 of current Application. All of the epitopes of HBV Pre-S antigenic peptides disclosed by Mimms et all are able to induce anti-pre-S1 and pre-S2 antibodies (see example 4). Therefore, it would have been obvious for a person with ordinary skill in the art to use any disclosed HBV preS antigen to do the recombinant fusion protein with TetC fragment.

Appellants further allergen that even Mimms et al. teaches several epitopes of HBV pre-S1 protein as a subunit antigen, which is able to induce an immune response, there would have been no obvious reason why a skilled person would have focused simultaneously and specifically on the disclosure relating to fragment C in Khan et al. and at the disclosure relating to specific pre-S1 fragment in Mimms et al.

Appellants' argument has been considered; however, it is not persuasive because art teaches that HBV surface antigen peptide vaccine needs to be modified for enhancing its immunogenicity and expression as evidenced by Shi et al.

Shi et al. teach that synthetic peptides, the third generation vaccines have been given great attention by any researches, as they usually possess antigenic determination without any toxic effects. For example, Hepatitis B virus surface antigen epitope have been thoroughly investigated so there was sound basis for the studies of peptide vaccine of HBV. However, the peptide is too small to elicit an efficient immune response against HBV infection. Several approaches have now been adopted to enhance the immunogenicity of peptide vaccine, for example of coupling to a carrier protein, or fusing an epitope gene with a carrier gene (See lines 1-26 on 1st col. Of page 933). Shi et al. further teach to use Cholera toxin B subunit (CTB) as a carrier protein to carry the HBS pre-S2 antigen by using a linker sequence which is generally used in the art as disclosed by Khan et al. (See lines 34-56 on 2nd col. of page 934). Therefore, Shi et al. reference does provide a motivation of using a carrier gene for expressing the short peptide antigen epitope of HBV and enhance the immunogenicity of HBV peptide vaccine.

Appellants also asserted that Shi 's reference teaches against any expectation of success in fusing pre-S sequence to carrier protein because Shi et al. disclose that an extremely low antibody titer is produced. Therefore, Appellants argue that examiner overlooked this.

Appellants' argument has been considered; however, it is not persuasive because examiner does not overlook this phenomenon. In Shi et al's reference, they analyze the low titer of the anti-Pre-S2 antibody could be caused with two possibilities. One is that they used low amount of fusion protein and another more important reason is the method for detecting the Pre-S2 antibodies with a low sensitivity as the microtiter plate used for the assay was coated with HBsAg particle prepared from HBV-infected patients' serum, which contains lower than 5% of M protein and L protein that contains Pre-S2 epitope. Shi et al. further teach that when they coated the plate with CTB-HBV PreS2 fusion protein, the titer of anti-PreS2 antibody reached to 1:1280 (See 1st paragraph of Section of Discussion on page 936-937). Nevertheless, none of the reason as motioned by Shi et al. is related to the linking HBV Pre-S antigen epitope to the carrier protein CTB.

Moreover, Shi emphasized that if the gene of PreS2 is fused to CTB gene at the 3' end, the fused gene can be highly expressed in E. Coli. The recombinant fusion protein in the culture supernatant also can be easily purified by affinity chromatography, and retains the antigenicity and immunogenicity of both CTB and HBV PreS2. Shi et al. further disclose that they fused 160 amino acid residues peptide to the CTB gene at the 3' end; the fused gene was efficiently expressed in the E Coli. and the chimeric protein was proven to retain the antigenicities of both CTB and the fused peptide. Therefore, Shi finally concluded that all of these features give a sound basis for the gene fusion system to be used in constructing a new generation of peptide-based vaccine (See the last paragraph on 937). Therefore, the cited reference of Shi et al. does show an expectation of success of fusing pre-S sequence to a carrier protein.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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August 8, 2003

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